(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 157 690 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
02.08.2006 Bulletin 2006/31

(51) Int Cl.:
A61K 9/28 *(2006.01)* ***A61K 31/277*** *(2006.01)*
A61K 31/55 *(2006.01)*

(21) Application number: **01401247.0**

(22) Date of filing: **15.05.2001**

(54) **Sustained release pharmaceutical composition**

Arzneimittelzusammensetzung mit verzögerter Wirkstoffabgabe

Composition pharmaceutique à libération prolongée

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR

(30) Priority: **26.05.2000 US 579878**

(43) Date of publication of application:
28.11.2001 Bulletin 2001/48

(60) Divisional application:
06114560.3

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EP 1 157 690 B1

Description

BACKGROUND OF THE INVENTION

[0001] Food effect is a well-known phenomenon that can adversely affect the pharmacokinetics of drug distribution in the body. As a result, many drugs have to be taken either in fasted or fed conditions to achieve the optimum effect. Well known examples include carbamazepine tablets (to be taken with meals), captopril tablets (to be taken one hour before meals), or azithromycin tablets (to be taken 2 hours after meal), while some other drugs remain unaffected by food, as amoxicillin for example.

[0002] For this reason, FDA recommends to test bioequivalency of drug products either under fasted or fed conditions, depending on the drug. Moreover, in the latter case the meal itself is standardized.

[0003] Little formulation work has been conducted to date in order to overcome this food effect disadvantage.

[0004] US-P-5529791 describes an extended release formulation of diltiazem pellets coated with either cellulosic or synthetic polymers, and absence of food effect is reported. However, no link is explained between the composition of the product and the absence of food effect.

[0005] Benziger et al., J.Pharm.Sci., 85,4, pp.407-410 (1996) compared the bioavailability of oxycodone formulated as an immediate release aqueous solution or as extended release tablets, under fasted or fed conditions and found a significant difference in availability of the solution while no difference could be observed with the extended release tablets. These authors related the absence of food effect to the use of extended release tablets rather than to any specific formulation parameter.

[0006] US-P-5879714 a drug and a water insoluble polymer are mixed into a molten carrier, preferably water-soluble. The only example provided in this patent consists in melting PEG 8000 at 120°C and dispersing nifedipine, stearic acid and Eudragit RSPO in it. After cooling, the solidified mixture is ground into granules. Heat sensitivity of many drugs seems is a major concern when considering applying the process thereto. Absence of food effect is not disclosed but it is indicated that hydrophilic matrix systems are said to be more likely to induce food effect than the disclosed formulation.

[0007] US-P-5580578 provides controlled release formulation having a coating consisting essentially in methacrylic copolymers, said coating having been oven cured. Examples disclose compositions comprising a core comprising thee active ingredient (e.g. hydromorphone hydrochloride), an intermediate layer comprising hydroxypropylmethylcellulose and the cured overcoat based on Eudragit. After oven curing, drug products tested clinically were found to be exempt of food effect (this was however not justified by formulation parameters). The coating is comprised of sustained release acrylic copolymers of the type Eudragit RS (comprising optionally Eudragit RL)

[0008] EP 0 192 321-A discloses an enteric coated allergan pharmaceutical composition. Example 2 thereof disclosed a B_2/Cultivated Rye coating.

[0009] None of the above documents teaches or suggests the present invention.

SUMMARY OF THE INVENTION

[0010] The invention relates to a novel sustained release pharmaceucical composition as set out in the appended claims.

[0011] The instant invention also provides a process for making a pharmaceutical composition, as set out in the appended claims. The invention further relates to use at a functional coating as set out in the claims.

DETAILED DESCRIPTION

[0012] The composition of the present invention may take the form of a coated tablet.

[0013] The core of said tablet comprises one or several pharmacologically active substances chosen from carbamazepine, verapamil, nifedipine, felodipine, amlodipine, diltiazem, oxibutynin, doxazocin, venlafaxin, captopril, enalapril, and fenofibrate. The absorption of these active substances is known to be influenced by food intake.

[0014] The core usually comprises from 20 to 80% of active ingredient. It also generally comprises 10 to 80% by weight of a gelling agent, which can be chosen among hydroxypropylmethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, xanthan gum, carbomer, carragheen, polyethyleneglycol and polyethylene oxide. The core may additionally comprise classical excipients, like (microcristalline) cellulose, lubricants, silicon dioxide, desintegrating agents, etc

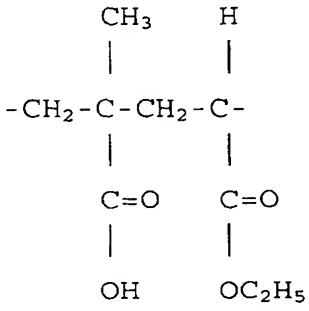
[0015] The core may be obtained by preparing a mixture of the starting compounds and direct compression. Alternatively, the gelling agent and the active ingredient are granulated together, and the resulting granules, optionally with other excipients, are compressed into a tablet.

[0016] Surprisingly, it has been discovered that the coating of the composition presents the unique feature of preventing the whole dosage form from being influenced by food intake.

[0017] This coating comprises a functional coating which comprises, based on the weight of the coating, from 30 to 80% of a gastroresistant polymer and from 10 to 40% of a hydrophilic silicon dioxide.

[0018] The gastroresistant polymer withstands the acidic medium of the stomach and the duodenum, but will dissolve in the intestines, as soon as the pH reaches a predetermined level (e.g. above 5.5 or above 7). This gastroresistant polymer can be selected from the group consisting in (uncured) poly(meth)acrylic acid, cellulose and alkylcellulose-phtalates. Molecular weight can vary within broad limits as will recognize the skilled man. The term "uncured" is used to differentiate over US-P-5580578.

[0019] Preferably, it is of the type of Eudragit L30D55. One preferred polymer is an anionic copolymer on the basis of methacrylic acid and acrylic acid ethyl ester. The formula is as follows:



[0020] The ratio free carboxyl group to ester group is preferably about 1:1. The mean molecular weight is e.g. about 250,000.

[0021] Such a copolymer will easily dissolve at pH values above 5.5 with the forming of salts.

[0022] Hydrophilic silicon dioxide is a known hydrophilic anti-tacking agent, the definition of which is known to the skilled man and can be found in the literature.

[0023] The functional coating may further comprise polyethyleneglycol, present in an amount from 5 to 30% by weight, based on the total weight of the functional coating. Stearic acid, dibutyl sebacate, propylene glycol and/or triethyl citrate can used in lieu of or in addition to polyethyleneglycol.

[0024] The functional coating usually represents from 0.5 to 6% by weight of the core weight.

[0025] The composition may further comprise an intermediate coating.

[0026] This coating which acts as a protecting layer comprises classical excipients, such as those recited above with respect to the core. For example, this intermediate coating may comprise hydroxypropylmethylcellulose and polyethyleneglycol. This intermediate coating usually represents from 0.1 to 3% by weight of the core weight. In the case of a layer comprised of HPMC and PEG, the weight ratio HPMC:PEG is e.g. from 2 to 10.

[0027] The composition of the invention is a sustained release; preferably it provides an effective release of the active ingredient for a period of at least 8 hours, preferably at least 12 hours.

[0028] The invention is also concerned with a process for preparing a pharmaceutical composition, comprising the step of coating a core comprising an active ingredient with the functional coating the core and coating being as defined above.

[0029] Thanks to the invention, it is now possible to avoid the food effect for the active ingredients mentioned. The process of the invention does not involve any heating step, in contrast with the prior art.

[0030] A precursor of the functional coating may be an aqueous dispersion (suspension) of a gascrvresistant polymer and of a hydrophilic silicon dioxide, present according to a weight ratio gastroresistant polymer:hydrophilic silicon between 0.75:1 and 8:1.

[0031] The dispersion (suspension) typically has a solid content from 3 to 50% by weight, e.g. about 10%.

[0032] The suspension may further comprise polyethyleneglycol dissolved in it, in an amount up to 15% by weight.

PREFERRED EMBODIMENTS

[0033] One preferred embodiment is a tablet comprising:

(a) a core comprising carbamazepine;
(b) a first layer comprising HPMC and polyethyleneglycol; and
(c) a second layer comprising a methacrylic copolymer, hydrophilic silicon dioxide and polyethyleneglycol.

EXAMPLES

[0034] The following examples illustrate the invention without limiting it.

Example 1. Carbamazepine.

[0035] The following core formulation was prepared

Ingredient	Amount per dosage unit (mg)
Carbamazepine	400.00
Aerosil 200®	3.00
Avicel PH 302®	100.00
Plasdone K90®	6.00
Denatured alcohol	290.00
Methocel K 100 LV®	125.00
Sodium stearylfumarate	17.00

[0036] Carbamazepine and Methocel® are mixed to Avicel and 50% of the amount of Aerosil 200® passed through a 0.5mm mesh size sieving screen. Plasdone® is dissolved in ethanol. The powder mixture is put into a mixer and wet with the solution. The resulting agglomerates are passed through a sieving screen of 0.062" (Co Mill®) . Granules are dried to constant weight in an oven at 45°C (loss on drying with infrared balance = 1.5%). Dry granules are mixed to sodium stearyl fumarate and Aerosil 200® in drum mixer (Turbula® T2C). The resulting mixture is pressed into tablets of 657 mg and about 150 N hardness, using a Manesty Betapress® tableting machine fitted with 12 mm diameter punches.

[0037] These tablet cores were then coated with an intermediate coating of the following composition:

Ingredient	Amount per dosage unit (mg)
Pharmacoat 603®	5.50
Polyethyleneglycol 1450	1.00
Purified water	50.00

[0038] Pharmacoat 603® is HPMC, available from Shin-Etsu chemicals. Pharmacoat 603 and PEG 1450 are dissolved in water and the solution is sprayed onto the tablet cores in a Vector coating pan, using the following spraying parameters:

Inlet Air Temperature	55 - 60C
Outlet Air Temperature	40 - 45C
Spray Rate	5 - 8g/minute
Spray Pressure	30 psi
Pan Speed	16 rpm

[0039] These coated tablets were then coated a second time with a functional coating of the following composition:

Ingredient	Amount per dosage unit (mg)
Eudragit® L30D55	13.30 (Solid*)
Syloid® 244FP	4.00
Polyethyleneglycol 8000	2.70

(continued)

Ingredient	Amount per dosage unit (mg)
Purified water	80.00
Eudragit® L30D55 is methacrylic copolymer available from Rohm. *the 13.3 value refers to the weight of the solid (rather than the weight of the dispersion).	

[0040] Syloïd® 244FP is hydrophilic silicon dioxide available from Grace Chemicals.

[0041] PEG 8000 is dissolved in 45% of amount of purified water. This solution is added to Eudragit suspension and stirred with paddle stirrer for 45 minutes. Syloïd® 244FP is suspended in the remaining part of water and the suspension is homogenized with a high-speed homogenizer Ultra Turrax® T25. The two suspensions are mixed and the mixture is sprayed onto the tablets in a Vector coating pan, using the following parameters:

Inlet Air Temperature	55 - 60C
Outlet Air Temperature	40 - 45C
Spray Rate	5 - 8g/minute
Spray Pressure	30 psi
Pan Speed	16 rpm

[0042] This coating is uncured, since no oven is used once the coating has been applied.

[0043] These tablets are tested for dissolution in standard apparatus type 1 of United States Pharmacopoeia. A 2% solution of sodium laurylsulfate in 0.01M potassium dihydrogenophosphate pH 6.8 buffer is used as dissolution medium. The amount of carbamazepine dissolved is recorded vs. time by using a Hewlett Packard HP8452A spectrophotometer. The curve is given in figure 1. It can be seen that the composition provides an effective release of carbamazepine during about 12 hours.

[0044] For the clinical trials, this formulation was tested against the same Tegretol® XR, reference product from Novartis® in a two way cross study performed on 6 healthy volunteers. To get an evaluation of the efficiency of the coating, tablets of the above formulation were also tested against tablets of the same composition except that the functional coating was replaced by a classical (cosmetic) coating of the following composition:

Ingredient	Amount per dosage unit (mg)
Opadry®	15.00
Purified water	80.00
Opadry® comprises HPMC, HPC, titanium dioxide and PEG; it is available from Coloron.	

[0045] Classical pharmacokinetics parameters Cmax and AUC were recorded, where:

- Cmax is the maximal plasma concentration reached during the study; and
- AUC is the area under the plasmatic concentration vs. time curve.

[0046] Results presented in table are ratios of parameters between test and reference products. Reference product is Tegretol® . Table 1 gives the results for the classical tablet while table 2 gives the results for the tablet of the invention.

Table 1

	$CmaX_{ref}$ /$CmaX_{test}$	AUC_{ref}/AUC_{test}
Fasted conditions	1.01	0.99
Fed conditions	1.48	1.26

Table 2

	$CmaX_{ref}/CmaX_{test}$	AUC_{ref}/AUC_{test}
Fasted conditions	1.03	1.06
Fed conditions	1.07	1.03

[0047] From the above tables, it is clear that the classical tablet has a marked food effect while the tablet of the invention are free of any food effect.

Example 2. Verapamil.

[0048] In a manner similar as above, the following formulation was prepared.

Core:

Ingredient	Amount per dosage unit (mg)
Verapamil HCl	240.00
Avicel PH 101	25.00
Plasdone K30®	20.00
HPMC 15,000 cPs	35.00
HPMC 100 cPs	20.00
Silicon dioxide	1.50
Magnesium stearate	3.50
HPMC is hydroxypropylmethylcellulose.	

Coating:

Ingredient	Amount per dosage unit (mg)
Eudragit® L30D55	7.50
Syloid® 244FP	3.00
PEG 1450	1.50

Example 3. Oxibutynin.

[0049] In a manner similar as above, the following formulation was prepared.

Core:

Ingredient	Amount per dosage unit (mg)
Oxibutynin HCl	15.00
Avicel PH 101	24.50
Plasdone K30®	10.00
Polyox WSR	180.00
Silicon dioxide	3.00
Sodium stearyl fumarate	6.00
Vitamin E	2.00

Coating:

Ingredient	Amount per dosage unit (mg)
Eudragit® L30D55	5.55
Fumed silica	2.20
PEG 1450	1.10
Triethyl citrate	0.55
Fumed silica is hydrophilic silicon dioxide available from Grace Chemicals. Triethyl citrate is a plasticizer.	

[0050] The dissolution profile has been determined (medium is 750 ml phosphate buffer pH=6.8, basket 100 rpm). The results are the following:

Time (hr)	% dissolved
1	11
2	20
4	38
6	54
8	70
10	83
12	99

Claims

1. A sustained release composition comprising:

   (a) a core comprising an active ingredient selected from the group consisting of carbamazepine, verapamil, nifedipine, felodipine, amlodipine, diltiazem, oxibutynin, doxazocin, venlafaxin, captopril, enalapril and fenofibrate: and
   (b) a functional coating comprising, based on the weight of the coating, from 30 to 80% of a gastroresistant polymer and from 10 to 40% of a hydrophilic silicon dioxide.

2. The composition according to claim 1, in which the gastroresistant polymer is selected from the group consisting in uncured poly(meth)acrylic acids, cellulose and alkylcellulose-phthalates.

3. The composition according to claim 1 or 2, in which the functional coating further comprises polyethyleneglycol, present in an amount from 5 to 30% by weight, based on the total weight of the functional coating.

4. The composition according to any one of claims 1 to 3, in which the functional coating represents from 0.5 to 6% by weight of the core weight.

5. The composition according to any one of claims 1 to 4, in which the core comprises from 20 to 80% of active ingredient.

6. The composition according to any one of claims 1 to 5, in which the core is comprised of granules compressed together.

7. The composition according to any one of claims 1 to 6, which further comprises an intermediate coating.

8. The composition according to claim 7, in which the intermediate coating comprises hydroxypropylmethylcellulose

and polyethyleneglycol.

9. The composition according to any one of claims 1 to 8, providing effective release of the active ingredient for a period of at least 8 hours.

10. A process for making a pharmaceutical composition, comprising the step of coating a core comprising an active ingredient selected from the group consisting of carbamazepine, verapamil, nifedipine, felodipine, amlodipine, diltiazem, oxibutynin, doxazocin, venlafaxin, captopril, enalapril and fenofibrate, with a functional coating comprising, based on the weight of the coating, from 30 to 80% of a gastroresistant polymer and from 10 to 40% of an hydrophilic silicon dioxide.

11. The process of claim 10, in which the composition is as defined in any one of claims 1 to 9.

12. Use of a functional coating, in the manufacture of a sustained release composition, the functional coating comprising, based on the weight of the coating, from 30 to 80% of a gastroresistant polymer and from 10 to 40% of a hydrophilic silicon dioxide to coat a core comprising an active ingredient selected from the group consisting of carbamazepine, verapamil, nifedipine, felodipine, amlodipine, diltiazem, oxibutynin, doxazocin, venlafaxin, captopril, enalapril and fenofibrate.

13. Use according to claim 12, in which the gastroresistant polymer is selected from the group consisting in uncured poly(meth)acrylic acids, cellulose and alkylcellulose-phthalates.

14. Use according to claim 12 or 13, in which the functional coating further comprises polyethyleneglycol, present in an amount from 5 to 30% by weight, based on the total weight of the functional coating.

15. Use according to any one of claims 12 to 14, in which the functional coating represents from 0.5 to 6% by weight of the core weight.

16. Use according to any one of claims 12 to 15, in which the core comprises from 20 to 80% of active ingredient.

17. Use according to any one of claims 12 to 16, in which the core is comprised of granules compressed together.

18. Use according to any one of claims 12 to 17, in which the composition further comprises an intermediate coating.

19. Use according to claim 18, in which the intermediate coating comprises hydroxypropylmethylcellulose and polyethyleneglycol.

20. Use of a functional coating in the manufacture of a sustained release composition, the functional coating comprising, based on the weight of the coating, from 30 to 80% of a gastroresistant polymer comprised of uncured poly(meth) acrylic acids and from 10 to 40% of a hydrophilic silicon dioxide,
to coat a core comprising an active ingredient selected from the group consisting of carbamazepine, verapamil, nifedipine, felodipine, amlodipine, diltiazem, oxibutynin, doxazocin, venlafaxin, captopril, enalapril and fenofibrate.

21. Use according to claim 20, in which the functional coating further comprises polyethyleneglycol, present in an amount from 5 to 30% by weight, based on the total weight of the functional coating.

22. Use of a functional coating in the manufacture of a sustained release composition, the functional coating comprising, based on the weight of the coating, from 30 to 80% of a gastroresistant polymer comprised of uncured poly(meth) acrylic acids, from 10 to 40% of a hydrophilic silicon dioxide and from 5 to 30% by weight of polyethyleneglycol, to coat a core comprising oxibutynin.

23. Use according to any one of claims 12 to 22, wherein the composition provides effective release of the active ingredient for a period of at least 8 hours.

Patentansprüche

1. Zusammensetzung mit verzögerter Freisetzung, umfassend:

(a) einen Kern, der einen Wirkstoff umfasst, der aus der aus Carbamazepin, Verapamil, Nifedipin, Felodipin, Amlodipin, Diltiazem, Oxibutynin, Doxazocin, Venlafaxin, Captopril, Enalapril und Fenofibrat bestehenden Gruppe ausgewählt ist, und
(b) eine funktionelle Beschichtung, die, bezogen auf das Gewicht der Beschichtung, von 30 bis 80 % eines gastroresistenten Polymers und von 10 bis 40 % eines hydrophilen Siliciumdioxids umfasst.

2. Zusammensetzung nach Anspruch 1, wobei das gastroresistente Polymer aus der aus ungehärteten Poly(meth) acrylsäuren, Cellulose- und Alkylcellulosephthalaten bestehenden Gruppe ausgewählt ist.

3. Zusammensetzung nach Anspruch 1 oder 2, wobei die funktionelle Beschichtung weiterhin Polyethylenglycol umfasst, das in einer Menge von 5 bis 30 Gew.-%, bezogen auf das Gesamtgewicht der funktionellen Beschichtung, vorhanden ist.

4. Zusammensetzung nach einem der Ansprüche 1 bis 3, wobei die funktionelle Beschichtung 0,5 bis 6 Gew.-% des Kerngewichts darstellt.

5. Zusammensetzung nach einem der Ansprüche 1 bis 4, wobei der Kern von 20 bis 80 % Wirkstoffe umfasst.

6. Zusammensetzung nach einem der Ansprüche 1 bis 5, wobei der Kern aus zusammengepressten Körnern besteht.

7. Zusammensetzung nach einem der Ansprüche 1 bis 6, die weiterhin eine Zwischenbeschichtung umfasst.

8. Zusammensetzung nach Anspruch 7, wobei die Zwischenbeschichtung Hydroxypropylmethylcellulose und Polyethylenglycol umfasst.

9. Zusammensetzung nach einem der Ansprüche 1 bis 8, die eine wirksame Freisetzung des Wirkstoffs für einen Zeitraum von wenigstens 8 h ergibt.

10. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, umfassend den Schritt der Beschichtung eines Kerns, der einen Wirkstoff umfasst, der aus der aus Carbamazepin, Verapamil, Nifedipin, Felodipin, Amlodipin, Diltiazem, Oxibutynin, Doxazocin, Venlafaxin, Captopril, Enalapril und Fenofibrat bestehenden Gruppe ausgewählt ist, mit einer funktionellen Beschichtung, die, bezogen auf das Gewicht der Beschichtung, von 30 bis 80 % eines gastroresistenten Polymers und von 10 bis 40 % eines hydrophilen Siliciumdioxids umfasst.

11. Verfahren nach Anspruch 10, wobei die Zusammensetzung in einem der Ansprüche 1 bis 9 definiert ist.

12. Verwendung einer funktionellen Beschichtung zur Herstellung einer Zusammensetzung mit verzögerter Freisetzung, wobei die funktionelle Beschichtung, bezogen auf das Gewicht der Beschichtung, von 30 bis 80 % eines gastroresistenten Polymers und von 10 bis 40 % eines hydrophilen Siliciumdioxids umfasst, zur Beschichtung eines Kerns, der einen Wirkstoff umfasst, der aus der aus Carbamazepin, Verapamil, Nifedipin, Felodipin, Amlodipin, Diltiazem, Oxibutynin, Doxazocin, Venlafaxin, Captopril, Enalapril und Fenofibrat bestehenden Gruppe ausgewählt ist.

13. Verwendung nach Anspruch 12, wobei das gastroresistente Polymer aus der aus ungehärteten Poly(meth)acrylsäuren, Cellulose- und Alkylcellulosephthalaten bestehenden Gruppe ausgewählt ist.

14. Verwendung nach Anspruch 12 oder 13, wobei die funktionelle Beschichtung weiterhin Polyethylenglycol umfasst, das in einer Menge von 5 bis 30 Gew.-%, bezogen auf das Gesamtgewicht der funktionellen Beschichtung, vorhanden ist.

15. Verwendung nach einem der Ansprüche 12 bis 14, wobei die funktionelle Beschichtung 0,5 bis 6 Gew.-% des Kerngewichts darstellt.

16. Verwendung nach einem der Ansprüche 12 bis 15, wobei der Kern von 20 bis 80 % Wirkstoffe umfasst.

17. Verwendung nach einem der Ansprüche 12 bis 16, wobei der Kern aus zusammengepressten Körnern besteht.

18. Verwendung nach einem der Ansprüche 12 bis 17, wobei die Zusammensetzung weiterhin eine Zwischenbeschichtung umfasst.

19. Verwendung nach Anspruch 18, wobei die Zwischenbeschichtung Hydroxypropylmethylcellulose und Polyethylenglycol umfasst.

20. Verwendung einer funktionellen Beschichtung zur Herstellung einer Zusammensetzung mit verzögerter Freisetzung, wobei die funktionelle Beschichtung, bezogen auf das Gewicht der Beschichtung, von 30 bis 80 % eines gastroresistenten, aus ungehärteten Poly(meth)acrylsäuren bestehenden Polymers und von 10 bis 40 % eines hydrophilen Siliciumdioxids umfasst, zur Beschichtung eines Kerns, der einen Wirkstoff umfasst, der aus der aus Carbamazepin, Verapamil, Nifedipin, Felodipin, Amlodipin, Diltiazem, Oxibutynin, Doxazocin, Venlafaxin, Captopril, Enalapril und Fenofibrat bestehenden Gruppe ausgewählt ist.

21. Verwendung nach Anspruch 20, wobei die funktionelle Beschichtung weiterhin Polyethylenglycol umfasst, das in einer Menge von 5 bis 30 Gew.-%, bezogen auf das Gesamtgewicht der funktionellen Beschichtung, vorhanden ist.

22. Verwendung einer funktionellen Beschichtung zur Herstellung einer Zusammensetzung mit verzögerter Freisetzung, wobei die funktionelle Beschichtung, bezogen auf das Gewicht der Beschichtung, von 30 bis 80 % eines gastroresistenten, aus ungehärteten Poly(meth)acrylsäuren bestehenden Polymers, von 10 bis 40 % eines hydrophilen Siliciumdioxids und von 5 bis 30 Gew.-% Polyethylenglycol umfasst, zur Beschichtung eines Oxibutynin umfassenden Kerns.

23. Verwendung nach einem der Ansprüche 12 bis 22, wobei die Zusammensetzung eine wirksame Freisetzung des Wirkstoffs für einen Zeitraum von wenigstens 8 h ergibt.

Revendications

1. Composition à libération prolongée comprenant :

   (a) un noyau comprenant un ingrédient actif choisi dans le groupe constitué des composés carbamazépine, vérapamil, nifédipine, félodipine, amlodipine, diltiazem, oxybutynin, doxazosine, venlafaxine, captopril, énalapril et fénofibrate ; et
   (b) un revêtement fonctionnel comprenant, sur la base du poids du revêtement, de 30 à 80 % d'un polymère gastrorésistant et de 10 à 40 % de dioxyde de silicium hydrophile.

2. Composition selon la revendication 1, dans laquelle le polymère gastro-résistant est choisi dans le groupe constitué des acides poly(méth)acryliques non durcis, de la cellulose et des phtalates d'alkylcellulose.

3. Composition selon la revendication 1 ou 2, dans laquelle le revêtement fonctionnel comprend en outre du polyéthylèneglycol, présent en une quantité de 5 à 30 % en poids, sur la base du poids total du revêtement fonctionnel.

4. Composition selon l'une quelconque des revendications 1 à 3, dans laquelle le revêtement fonctionnel représente de 0,5 à 6 % en poids du poids du noyau.

5. Composition selon l'une quelconque des revendications 1 à 4, dans laquelle le noyau comprend de 20 à 80 % d'ingrédient actif.

6. Composition selon l'une quelconque des revendications 1 à 5, dans laquelle le noyau est constitué de granulés compressés ensemble.

7. Composition selon l'une quelconque des revendications 1 à 6, qui comprend en outre un revêtement intermédiaire.

8. Composition selon la revendication 7, dans laquelle le revêtement intermédiaire comprend de l'hydroxypropylméthylcellulose et du polyéthylèneglycol.

9. Composition selon l'une quelconque des revendications 1 à 8, permettant d'obtenir une libération efficace de l'ingrédient actif pendant une durée d'au moins 8 heures.

10. Procédé de fabrication d'une composition pharmaceutique, comprenant l'étape de revêtement d'un noyau comprenant un ingrédient actif choisi dans le groupe constitué des composés carbamazépine, vérapamil, nifédipine, félo-

dipine, amlodipine, diltiazem, oxybutynin, doxazosine, venlafaxine, captopril, énalapril et fénofibrate, avec un revêtement fonctionnel comprenant, sur la base du poids du revêtement, de 30 à 80 % d'un polymère gastrorésistant et de 10 à 40 % de dioxyde de silicium hydrophile.

11. Procédé selon la revendication 10, dans lequel la composition est telle que définie dans l'une quelconque des revendications 1 à 9.

12. Utilisation d'un revêtement fonctionnel, dans la fabrication d'une composition à libération prolongée, le revêtement fonctionnel comprenant, sur la base du poids de revêtement, de 30 à 80 % d'un polymère gastrorésistant et de 10 à 40 % de dioxyde de silicium hydrophile pour revêtir un noyau comprenant un ingrédient actif choisi dans le groupe constitué des composés carbamazépine, vérapamil, nifédipine, félodipine, amlodipine, diltiazem, oxybutynin, doxazosine, venlafaxine, captopril, énalapril et fénofibrate.

13. Utilisation selon la revendication 12, dans laquelle le polymère gastro-résistant est choisi dans le groupe constitué des acides poly(méth)acryliques non durcis, la cellulose et les phtalates d'alkylcellulose.

14. Utilisation selon la revendication 12 ou 13, dans laquelle le revêtement fonctionnel comprend en outre du polyéthylèneglycol, présent en une quantité de 5 à 30 % en poids, sur la base du poids total du revêtement fonctionnel.

15. Utilisation selon l'une quelconque des revendications 12 à 14, dans laquelle le revêtement fonctionnel représente de 0,5 à 6 % en poids du poids du noyau.

16. Utilisation selon l'une quelconque des revendications 12 à 15, dans laquelle le noyau comprend de 20 à 80 % d'ingrédient actif.

17. Utilisation selon l'une quelconque des revendications 12 à 16, dans laquelle le noyau comprend des granulés compressés ensemble.

18. Utilisation selon l'une quelconque des revendications 12 à 17, dans laquelle la composition comprend en outre un revêtement intermédiaire.

19. Utilisation selon la revendication 18, dans laquelle le revêtement intermédiaire comprend de l'hydroxypropylméthylcellulose et du polyéthylèneglycol.

20. Utilisation d'un revêtement fonctionnel dans la fabrication d'une composition à libération prolongée, le revêtement fonctionnel comprenant, sur la base du poids du revêtement, de 30 à 80 % d'un polymère gastrorésistant constitué d'acides poly(méth)acryliques non durcis et de 10 à 40 % de dioxyde de silicium hydrophile, pour revêtir un noyau comprenant un ingrédient actif choisi dans le groupe constitué des composés carbamazépine, vérapamil, nifédipine, félodipine, amlodipine, diltiazem, oxybutynin, doxazosine, venlafaxine, captopril, énalapril et fénofibrate.

21. Utilisation selon la revendication 20, dans laquelle le revêtement fonctionnel comprend du polyéthylèneglycol, présent en une quantité de 5 à 30 % en poids, sur la base du poids total du revêtement fonctionnel.

22. Utilisation d'un revêtement fonctionnel dans la fabrication d'une composition à libération prolongée, le revêtement fonctionnel comprenant, sur la base du poids du revêtement, de 30 à 80 % d'un polymère gastrorésistant constitué d'acides poly(méth)acryliques non durcis, de 10 à 40 % de dioxyde de silicium hydrophile et de 5 à 30 % en poids de polyéthylèneglycol, pour revêtir un noyau comprenant de l'oxybutynin.

23. Utilisation selon l'une quelconque des revendications 12 à 22, dans laquelle la composition permet d'obtenir une libération efficace de l'ingrédient actif pendant un temps d'au moins 8 heures.